Proposed Decision Memo for Microvolt T-wave Alternans (CAG-00293N)

Decision Summary

CMS is seeking public comment on our proposed determination that there is sufficient evidence to conclude that the use of microvolt T-wave Alternans (MTWA) diagnostic testing is reasonable and necessary for the evaluation of Medicare beneficiaries at risk for sudden cardiac death (SCD). We are also proposing that MTWA diagnostic testing is only reasonable and necessary if measured employing the spectral analytic method.

We propose to issue a National Coverage Determination (NCD) that states: Microvolt T-wave Alternans diagnostic testing is covered for the evaluation of patients at risk of sudden cardiac death, only when the spectral analytic method is used.

We are requesting public comments on this proposed determination pursuant to section 731 of the Medicare Modernization Act. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

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Proposed Decision Memo

TO: Administrative File: CAG #00293
Microvolt T-wave Alternans Testing

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SUBJECT: Proposed Decision Memorandum for Microvolt T-wave Alternans Testing
DATE: December 21, 2005

I. Proposed Decision

CMS is seeking public comment on our proposed determination that there is sufficient evidence to conclude that the use of microvolt T-wave Alternans (MTWA) diagnostic testing is reasonable and necessary for the evaluation of Medicare beneficiaries at risk for sudden cardiac death (SCD). We are also proposing that MTWA diagnostic testing is only reasonable and necessary if measured employing the spectral analytic method.

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II. Background

Cardiovascular disease is the single most common cause of death in the United States. Sudden cardiac death (SCD) is estimated to account for approximately 50% of all cardiovascular deaths. This represents an estimated 350,000 cases per year and only about 20% of these patients survive to hospital discharge. Ventricular tachyarrhythmic events (VTE) are the mechanism responsible for 75-80% of these deaths. [1]

Microvolt T-wave alternans (MTWA) testing is a non-invasive diagnostic test that detects minute electrical activity in a portion of the electrocardiogram (EKG) know as the T-wave. Published articles in medical journals have proposed that MTWA testing has a role in the risk stratification of patients who may be at risk for sudden cardiac death (SCD) from ventricular arrhythmias.

Within patient groups that may be considered candidates for implantable cardioverter defibrillator (ICD) therapy, published literature indicates that a negative MTWA test may be useful in identifying low-risk patients who are unlikely to benefit from, and who may experience worse outcomes from, ICD placement.

The test is performed by placing high-resolution electrodes, designed to reduce electrical interference, on a patient's chest prior to a period of controlled exercise. These electrodes detect tiny beat-to-beat changes, on the order of one-millionth of volt, in the EKG T-wave. Spectral analysis is used to calculate these minute voltage changes. Spectral analysis is a sensitive mathematical method of measuring and comparing time and the electrocardiogram signals. Software then analyzes these microvolt changes and produces a report to be interpreted by a physician.

In a January 27, 2005 final decision memorandum for ICDs, CMS stated:

"We do strongly encourage the inclusion of MTWA is subsequent clinical trials, registries and other data collection protocols in order to further evaluate this promising risk-stratification technology and will work with the stakeholders involved in the subsequent data collection systems to include this information. CMS will continue to support these studies that collect this type of information."

III. History of Medicare Coverage

Medicare is a defined benefit program. An item or service must fall within a benefit category as a prerequisite to Medicare coverage. § 1812 (Scope of Part A); § 1832 (Scope of Part B) § 1861(s) (Definition of Medical and Other Health Services). MTWA may be eligible for coverage under the Social Security Act section 1861(s)(3) "other diagnostic tests".

CMS does not currently have an NCD on MTWA testing. Coverage is at local Medicare contractor discretion.

IV. Timeline of Recent Activities

July 5, 2005	CMS meets with the requestor, Cambridge Heart.
July 7, 2005	CMS opens an NCD to evaluate the use of MTWA testing in the Medicare population. CMS begins a national coverage determination review in response to an external request. A 30-day public comment period is opened.
August 5, 2005	Public comment period closes. CMS completes the posting of public comments to the coverage website.
December 21, 2005	Draft decision memorandum posted.

V. FDA Status

The Food and Drug Administration (FDA) has cleared Heartwave™ alternans devices, along with various software packages used to perform MTWA testing, through the 510(k) clearance process. Clearance was obtained on July 16, 2002 (K022152) and November 17, 2002 (K03564).

VI. General Methodological Principles

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service falling within a benefit category is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. The critical appraisal of the evidence enables us to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients. Improved net health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, and the blinding of readers of the index test, and reference test results.

A detailed account of the methodological principles of study design that agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B.

VII. Evidence

A. Introduction

We are providing a summary of the evidence we considered during our review. We will, of course, consider additional evidence submitted through the public comment period. The evidence reviewed to date in this proposed decision memorandum includes the published medical literature on pertinent clinical trials of MTWA.

B. Discussion of Evidence Reviewed

1. Questions

1. *Is the quality of evidence adequate to conclude that MTWA testing can improve net health outcomes and is reasonable and necessary for Medicare patients who are candidates for ICD placement?*

2. *If the evidence is adequate to conclude that MTWA testing can improve net health outcomes, what characteristics of the test method, the pathologic condition, or the patient can satisfactorily predict an improved health outcome?*

2. External technology assessments

We did not request an external technology assessment (TA) on this issue. CMS reviewed a (TA) published in October 2005 by the National Blue Cross and Blue Shield Association's Technology Evaluation Center (BCBSA TEC) entitled "Microvolt T-wave alternans testing to risk stratify patients being considered for ICD therapy for primary prevention of sudden death". That assessment concluded that MTWA did not meet BCBSA TEC criteria for coverage. The committee felt that the evidence was insufficient to permit conclusions regarding the effect on health outcomes, the evidence was insufficient to determine whether the use of MTWA improved net health outcomes or whether it is as beneficial as any established alternatives, and the use of MTWA to improve outcomes in the investigational setting had not been established.

3. Internal technology assessments

Literature search methods

The reviewed evidence was gathered from: 1) articles submitted by the requestor; 2) an existing technology assessment, and 3) a literature search of the PubMed database.

To support their request for coverage, the requestor submitted a listing of 1028 citations on a compact disc entitled "Publications and Abstracts: Clinical Compendium". These citations included articles on technical feasibility, mathematical models, animal studies, pediatric populations, pharmacologic interventions, and applications of MTWA for other than the requested indication (e.g., hypertension, cardiac pacing). Along with the list of 1028 citations was a separate "Table of Contents" of recent publications relevant to the coverage request. From this list, CMS excluded poster presentations, oral presentations, editorials, review articles, studies that did not specifically address MTWA as a risk stratifier for patients eligible for ICD treatment, and those lacking sufficiently detailed information on study design or discussion of results. From this "Table of Contents", and following a discussion with the requestor, 12 of the submitted articles were considered for review. Bibliographies of these publications were reviewed to identify additional relevant articles.

The limits of our PubMed search excluded non-English articles, studies with fewer than 10 cases, and those not involving human subjects. The search terms used were:

- T-wave alternans, arrhythmia
- T-wave alternans, ventricular
- T-wave alternans, implantable cardioverter defibrillator (ICD)
- T-wave alternans, cardiac defibrillator (ICD)
- T-wave alternans, (MADIT) II
- T-wave alternans, sudden cardiac death
- T-wave alternans, ejection
- T-wave alternans, infarction
- T-wave alternans, cardiomyopathy
- T-wave alternans, primary prevention

From the initial PubMed yield, CMS then applied the same exclusion criteria described above. Using these terms and exceptions, CMS did not identify any additional articles to those supplied by the requestor.

Evidence Review

A number of studies evaluating the effectiveness of MWTA have been found in the medical literature. These include studies evaluating MWTA in patients with ischemic cardiomyopathies, non-ischemic dilated cardiomyopathies, as well as in patients with mixed cardiomyopathies. Endpoints studied include morbidity, mortality (e.g., sudden cardiac deaths, VTE, as well as quality of life measures. Evaluations ranged from single prospective studies to systematic reviews (meta-analysis and article reviews).

Gehi and associates recently performed a meta-analysis evaluating the use of MTWA in determining risk stratification of VTE across a wide range of patient populations (Gehi, Stein, Metz, Gomes, 2005). Using PubMed and Cochrane databases to identify published articles performed between January 1990 and December 2004, 19 prospective studies, which included 2,608 subjects, were found which met the following inclusion criteria: 1) prospective cohort studies of greater than 10 subjects who underwent exercise induced MTWA testing for the prediction of SCD or ventricular arrhythmias; 2) provided primary data on results of MTWA and of clinical outcomes including SCD, cardiac death, ventricular arrhythmias, and/or implantable cardioverter defibrillator (ICD) shock; 3) provided clear definition of normal or abnormal MTWA testing; and 4) had a follow-up time of six months or longer. Outcomes of each study were presented as Positive Predictive Value (PPV), Negative Predictive Value (NPV), and univariate Relative Risk (RR) with Confidence Intervals (CIs) of MTWA for the prediction of ventricular arrhythmic events at follow up.

Study sample sizes ranged from 16 to 834 participants. The mean age of the subjects in the 19 studies ranged from 25 to 64 years, and the average follow-up was 21 months. There was a wide range of subject populations including congestive heart failure (CHF), ischemic CHF, non-ischemic CHF, post myocardial infarction (MI), athletes, and healthy subjects**.** Mean ejection fraction (EF) of study participants ranged from 23 to 71. After excluding all subjects with indeterminate MTWA test, the PPV at follow-up ranged from 0% to 67%, while the NPV ranged from 71 to 100%. The RR for having a cardiac event ranged from 0.85 to infinity.

For the 19 studies the summary PPV during the 21 months of follow-up was 19.3% (95% CI 17.7% to 21%); the NPV was 97.2% (95% CI 95.5% to 97.9%), and the univariate RR was 3.77 (95% CI 2.39 to 5.95). The study found that the presence of significant MTWA predicted nearly a four-fold risk of VTE compared to the absence of significant MTWA. The absence of MTWA carries a 3% risk of arrhythmic events during an average 21 months of follow-up. The study also revealed that there was no significant difference in PPV, NPV, or RR of MTWA testing between subjects with ischemic and non-ischemic CHF, as well as no significant difference in the NPV or RR of MTWA testing between CHF and post-MI subjects.

Three studies performed a multivariate Cox regression analysis to determine the independent predictive value of commonly used tests for risk stratification of arrhythmic events. In these three studies, MTWA was independently predictive of arrhythmic events.

In Gehi's assessment of all the articles included in the analysis, none of the studies were of poor quality, testing revealed appropriate heterogeneity, and no evidence of publication bias was found. In this review MTWA was absent in 25% to 54% of subjects, which the author felt was a significant portion of subjects.

Gehi noted that there were some limitations of this meta-analysis including, insufficient data in the multivariate analysis to determine the incremental prognostic value of MWTA independent of other predictors of arrhythmic events, the endpoints of the individual studies used in the summary calculations were variable, most of the subjects included in these studies were primarily men (making the results difficult to generalize to females), and the inconsistency in the exclusion of subjects using beta-blockers or anti-arrhythmic medications.

One of the first clinical studies that was able to demonstrate that electrical alternans was a marker for vulnerability for ventricular arrhythmias was performed by Rosenbaum and associates (Rosenbaum, Jackson, Smith, Garan, Ruskin, Cohen, 1994). The study consisted of 83 consecutive patients who were sent for diagnostic electrophysiologic studies and who met entry criteria (excluded if atrial pacing was not possible; if a permanent pacemaker had been previously implanted; or if excessive ventricular ectopic beats were present). Baseline measurements of electrical alternans were compared with the results of baseline electrophysiologic testing in each patient, along with the relation of electrical alternans to arrhythmia-free survival. Of the 83 patients that entered the study, 17 were excluded from the survival analysis because anti-arrhythmic drug therapy was initiated or changed during the follow-up period.

Of the 66 patients followed for up to 20 months, 13 had arrhythmic events (5 of the events were SCD, the remainders were ventricular arrhythmias). The level of T-wave alternans was significantly greater in patients who had arrhythmic events than in patients without events. This study also revealed that two independent predictors of inducible ventricular arrhythmias were repolarization alternans (ST-segment or T-wave alternans), and impaired left ventricular function. Further studies using multivariate analysis showed that repolarization alternans identified underlying electrical instability, independent of structural heart disease.

Subsequent studies have confirmed the role of T-wave alternans as a predictor for VTEs. Gold and associates compared T-wave alternans, signal-averaged electrocardiography (SAE), and programmed ventricular stimulation for arrhythmia risk stratification in patients undergoing electrophysiologic studies (Gold, Bloomfield, Anderson, El-Sherif, Wilber, et al. 2000). This study was initiated because the authors felt that accurate identification of patients at increased risk for sustained ventricular arrhythmias was critical to prevent sudden cardiac death. They felt that T-wave alternans correlated with arrhythmia vulnerability, but at that point in time, SAE and programmed ventricular stimulation were more commonly used for risk stratification of this condition. This prospective, multicenter study consisted of 313 participants who underwent diagnostic electrophysiologic studies for T-wave alternans testing using a spectral analysis algorithm. Programmed ventricular stimulation as well as signal averaged electrocardiography were also performed. The primary endpoint was the occurrence of a VTE, while secondary endpoints included a VTE or all-cause mortality. Based on the Kaplan Meier survival analysis as the primary endpoint, MTWA predicted events with a RR of 10.9 compared to RR of 7.1 and 4.5 as predicted by programmed ventricular stimulation, and SAE respectively. The RR for secondary endpoints were 13.9, 4.7 and 3.3 respectively also. When comparing statistical performance of the noninvasive test to predict the results of programmed ventricular stimulation during electrophysiological testing, MTWA and SAE resulted in the following:

	Sensitivity	Specificity	PPV	NPV	RR	p-value
MTWA	77.8%	72.5%	42.9%	92.5%	5.7	<0.0001
SAE	55.6%	83.3%	46.9%	87.5%	3.8	<0.0001

To assess the independent predictors of clinical events, a multivariate analysis was performed based on 11 of the clinical parameters. MTWA was identified as the only independent predictor of cardiac events. Compared to SAE, MTWA was a more sensitive predictor of the induction of a sustained VT during programmed ventricular stimulation, as well as a better discriminator of VTEs or death.

Hohnloser and colleagues also evaluated MTWA's usefulness in predicting VTEs in patients with dilated cardiomyopathies (Hohnloser, Klingenheben, Bloomfield, Dabbous, Cohen 2003). This study used consecutive patients referred to a heart failure clinic for management of their condition, or to the electrophysiologic laboratory for evaluation of symptomatic arrhythmias. Inclusion criteria for the study included a diagnosis of dilated cardiomyopathy, no intercurrent illnesses limiting life expectancy, and the presence of sinus rhythm at initial presentation. Risk stratification was performed at entry, and assessment included determination of left ventricular ejection fraction (LVEF), heart rate variability, mean 24-hour RR interval, presence of non-sustained VT (NSVT), baroreflex sensitivity (BRS), and analysis of signal-averaged electrocardiography (SAE). Patients at high risk were defined by: LVEF $\leq$35%; mean RR $\leq$700 ms; HR variability; standard deviation of normal-to-normal intervals $\leq$70 ms (SDNN); and BRS $\leq$3.0 ms/mm Hg. An intraventricular conduction defect (IVCD) was defined as a QRS duration of $\geq$ 120 ms. Endpoints included sudden cardiac death (SCD), cardiac arrest due to VF, hemodynamically unstable VT or VF.

A total of 137 patients with non-ischemic dilated cardiomyopathy were included in the study (31 females, and 106 males with a mean age of 55). At study entry 37 patients (27%) had been fitted with an ICD because of prior history of cardiac arrest, documented sustained VT, syncope, or for prophylactic reasons. Patients were followed for 18 months. MTWA, using a spectral analysis algorithm, was positive in 66 patients (48%), negative in 34 patients (25%), and indeterminate in 37 (27%). A multivariate analysis was performed looking at the outcomes of the various risks stratification methods. Results of the analysis revealed that MTWA was the only independent statistical predictor of arrhythmic events (X^2 of 3.87). In patients with ICDs versus those without ICDs, the number of persons with positive MTWA test was 23 (62%) versus 43 (43%), and the number with a negative MTWA test results was 5 (14%) versus 29 (29%) (both numbers were statistically significant), and the number with indeterminate test was 9 (24%) versus 28 (28%) which was not statistically significant. The author concluded that the study demonstrated that MTWA positive patients are at particularly high risk for VTEs. Limitations of the study noted by the authors included a high number of patients enrolled in the study after receiving an ICD, and only including hemodynamically unstable VTEs as endpoints in these ICD recipients.

	Sensitivity	Specificity	PPV	NPV	RR	p-value
MTWA	87%	37%	22%	94%	3.4	<0.0001
SAE	47%	63%	17%	88%	1.4	<0.0001
LVEF≤ 35%	80%	21%	15%	86%	1.0	

A number of other studies have evaluated the use of MTWA in patients with dilated cardiomyopathies. Kitamura and colleagues prospectively followed 104 patients with dilated cardiomyopathy (mean age 52 years) to determine the prognostic value of onset heart rate (OHR) in MTWA (using a spectral analysis algorithm) in patients with non-ischemic dilated cardiomyopathy (Kitamura, Ohnishi, Okajima, Ishida et al. 2002). All patients were in sinus rhythm and dilated cardiomyopathy was clinically diagnosed according to the criteria recommended by the World Health Organization and the National Heart, Lung, and Blood Institute. To define the high risk subgroup, MTWA positive patients were categorized according to a predetermined cut-off point of OHR for MTWA of ≤100 beats/min which represented the division between the two groups (group A consisted of patients with OHR ≤100 beats/min and group B with 100 < OHR ≤110). MTWA negative patients were designated group C. Conventional markers including left ventricular end-diastolic diameter (LVDd) left ventricular ejection fraction (LVEF), non-sustained ventricular tachycardia (NSVT), SAE were used for comparison purposes. Endpoints included sudden cardiac death (SCD), or documented SVT/VF. Forty-six of the patients (44%) were MTWA positive, while 37 (36%) were MTWA negative. The remainder 21 (20%) were MTWA indeterminate. After excluding patients for poor electrocardiogram recordings, only 83 patients remained in the study. Of the 46 MTWA positive patients, 24 were categorized in group A, while 22 were in group B. Both groups were comparable in terms of heart rate, and the OHR of MTWA was not significantly correlated with LVEF (r=0.025). There were 9 cardiac events in group A, and 2 cardiac events in group B. Only 1 cardiac event occurred in group C. Further analysis revealed that the determination of OHR in combination with MTWA could identify the high risk subgroup among the 83 patients with dilated cardiomyopathy. Using multivariate Cox hazard analysis, the study revealed that MTWA with OHR ≤100 beats/min and left LVEF were the only independent predictors of arrhythmic events.

	Sensitivity	Specificity	PPV	NPV	RR
MTWA	91.7%	50.7%	23.9%	97.3%	8.8
SAE	41.7%	78.9%	25%	88.9%	2.3
LVEF≤ 35%	66.7%	66.2%	25%	92.2%	3.2

Adachi and associates also studied the use of MTWA as a risk stratification tool in patients with dilated cardiomyopathy (Adachi, Ohnishi, Yokoyama 2001). This study consisted of 82 consecutive patients with a diagnosis of non-ischemic dilated cardiomyopathy that were referred for electrophysiologic studies. MTWA testing was performed, as well as left ventricular end-diameter (LVDd), left ventricular ejection fraction (LVEF), signal-average ECG (SAECG), 24 hour Holter monitoring for non-sustained VT (NSVT), as well as QT dispersion (QTd) for comparison purposes. Endpoints included sudden cardiac death (SCD), documented SVT, or resuscitated VF. The follow-up period lasted for 24 months. In this study, 37% of participants were MTWA positive, 41% were MTWA negative, and the remaining 22% were indeterminate. The percentage of patients with MTWA in the arrhythmic events group (group A) was significantly larger than that in the non-event group (group B) (90% versus 39%). When evaluating MTWA and other predictor markers for event-free survival, the following matrix is created:

	Sensitivity	Specificity	PPV	NPV	RR	p-values
MTWA	90%	61%	30%	97%	10.2	0.0029
SAE	40%	80%	27%	88%	2.2	0.1783
LVEF≤ 35%	70%	80%	39%	93%	6.0	0.0013

A multivariate Cox regression analysis revealed that a combination of an LVEF of ≤35% along with MTWA positivity were the only statistically significant independent risk factors for VTEs. None of the patients who were MTWA negative and who had an LVEF>35% experienced arrhythmic events. The author did note that small sample size, as well as the exclusion of patients from the study due to atrial fibrillation, were some limitations of this study.

Momiyama and associates evaluated MTWA using a spectral analysis algorithm as a marker of high risk in patients with hypertrophic cardiomyopathy (HCM), comparing 14 patients with HCM to 9 normal controls (Momiyama, Hartikainen, Nagayoshi, Albrecht et al. 1997). Risk stratification for VTEs had been made prior to the study based on an adverse family history, the detection of VT on ambulatory electrocardiogram monitoring, and the finding of paced ventricular electrograms. Of the 14 patients with HCM, 7 were classified as high risk for VTEs, while the other 7 were determined to be of low risk. Nine healthy volunteers made up the control group. There were no significant differences in age or gender in the 3 groups. MTWA voltage was used as a measure (defined as >1.9μV during a period of >250 betas with a HR >100 beats/min), while VTEs, and sudden cardiac death (SCD) were chosen as endpoints. The results of the alternans analysis revealed that the alternans voltage was significantly higher in the high-risk group than in the low-risk and control groups (2.8+/-1.7 vs 0.6+/-0.5). In the high-risk group, the median alternans ratio was also significantly greater than in the low-risk group as well as the control group (3.9 vs 0.6 and 0.3). Of the 7 high-risk participants, 5 (71%) showed significant MTWA voltage (3.7+/-1.0), whereas none of the 7 low-risk patients or the 9 control subjects had MTWA 1.9μV. Of particular note, the study documented that all 4 patients with sustained VT or abnormal paced ventricular electrograms exhibited MTWA. Limitations of the study included small sample size, the inability to elucidate the quantitative relationship between MTWA, and the inhomogeneity of intramyocardial conduction assessed by electrophysiologic testing because it was performed in only 6 of 14 patients.

A number of studies have evaluated the usefulness of MTWA as a predictor of cardiac events after a myocardial infarction (MI). Ikeda and associates used a combined assessment of MTWA and other predictive test to predict arrhythmias after myocardial infarction (Ikeda, Sakata, Takami, Kondo et al. 2000), and later with other collaborators Ikeda used MTWA as a predictor for sudden cardiac death after myocardial infarction (Ikeda, Saito, Tanno, Shimizu, 2000). In the first study, 102 consecutive patients with an acute MI were followed longitudinally, comparing MTWA, late potentials (LP) by SAE, and ejection fractions (EF) for the detection of arrhythmic events (LP as determined by SAE, and left ventricular ejection fraction have been used to identify patients at risk for the development of ventricular arrhythmias). Documentation of spontaneous ventricular arrhythmic events was uses as an endpoint in this study. The follow-up period for the study was 13 months. The results of the study revealed that MTWA was present in 50 patients (49%), while LP was present in 21 patients (21%) and an ejection fraction of less than 40% in 28 patients (27%). Using predictive values as well as a univariate Cox regression to predict events, the following accuracy measures were obtained for the three diagnostic measures:

	Sensitivity	Specificity	PPV	NPV	RH	p-value
MTWA	93%	59%	28%	98%	16.8	0.006
LP	53%	85%	38%	91%	5.7	0.0008
EF	60%	78%	32%	92%	4.7	0.004

The authors concluded that because of the high values for sensitivity as well as negative predictive value, MTWA could be used as a tool for screening patients for various serious ventricular arrhythmias after a myocardial infarction. The author notes that some limitations of the study include the fact that patients with a very low EF (<20%) were excluded from the study. Also the results may not be applicable to patients with significant accounts of ventricular ectopy or abnormal heart rate variability.

In a second study, Ikeda and associates again assessed T-wave alternans as a predictor for sudden cardiac death after an MI (Ikeda, Saito, Tanno, Shimizu, Watanabi, Ohnishi, et al. 2002). This was a prospective study that recruited 850 consecutive MI patients. Most of the participants (90%) underwent MTWA testing within 2 to 10 weeks of the acute MI. In addition to MTWA, other prognostic indices used to predict sudden death included ventricular late potentials (LP), and 40% left ventricular ejection fraction (EF). Primary endpoints were prospectively defined as sudden cardiac death (SCD), as well as VTE. Secondary endpoints included sustained tachycardia. During the study a number of participants died from non-arrhythmic causes. For the remaining 834 patients, the mean follow-up period was 25 months. A total of 67 patients (8%) had arrhythmic events (either primary or secondary endpoints). Of these patients, 3% reached 1 of the primary endpoints, 12 died suddenly, and 13 had resuscitated VF while for secondary endpoints, 5% had sustained VT. MTWA was positive in 36% of participants, indeterminate in 12% and negative in 52% of participants. LP was positive, and an abnormal EF was found in 18% of participants, and LP was negative and the EF was normal in remaining 82% of participants. Of the 11 risk indices (e.g., gender, age, CABG, antiarrhythmic drug therapy, successful percutaneous coronary intervention, LP, MTWA, EF), univariate analysis revealed that MTWA predicted primary endpoints with a relative hazard ratio of 11.4, while the remainder risk indices had relative risk ratios varying between 6.6 and 3.2. Using multivariate Cox regression, only MTWA and EF were found to be significantly associated with primary endpoints. MTWA has the highest sensitivity and NPV than either EF alone, or combined MTWA and EF.

	Sensitivity	Specificity	PPV	NPV	RH	p-value
MTWA	92%	83%	7%	99%	11.4	0.0001
EF	56%	83%	9%	98%	6.6	0.0001
MTWA/EF	52%	92%	18%	98%	11.9	0.0001
	50%	84%	10%	98%	5.2	0.0002

The authors concluded that MTWA and abnormal left ventricular ejection fraction were significant predictors of sudden cardiac death or VF, where as LP by signal-averaged electrocardiography and other prognostic indices failed to predict subsequent risk in this large series of infarction survivors. One of the limitations of the study mentioned by the authors is not including heart rate variability as a study variable. In both studies, a spectral analysis algorithm was used as a protocol for MTWA testing.

Because of the association between VTEs and cardiac mortality, implanted cardiac defibrillators have been used in patients at high risk of this condition. In 2003, CMS recommended using QRS duration as a means to identify MADIT II-like patients suitable for implanted cardiac defibrillators (ICD) therapy. Bloomfield and associates compared the ability of MTWA (using a spectral analysis algorithm) and QRS duration to identify groups at high risk and low risk of dying among heart failure patients who met the MADIT II criteria for ICD prophylaxis (Bloomfield, Steinman, Namerow, Parides, Davidenko, Kaufman, et al. 2004). The study enrolled 549 subjects, of whom 177 had ischemic heart disease and an ejection fraction of $\leq$ 30 percent, and also met other MADIT II criteria (> than 1 month after a myocardial infarction, and > 3 months after coronary revascularization). MTWA testing as well as QRS testing was performed on each participant, and all-cause mortality was used as an endpoint. Based on the results of these test, participants were placed in 1 of 4 groups: MTWA normal; MTWA abnormal; QRS < 120 ms; QRS >120 ms. The results of the study revealed the following: 32% of the MADIT II-like patients had a QRS duration of >120 ms, and the MTWA test was abnormal in 68% of the patients. The 2-year actuarial mortality rates for patients with positive and indeterminate MTWA test were similar (14.5% and 20.1% respectively). For all 177 MADIT II-like patients, the 2-year actuarial mortality rate was 13.2%. When analyzing the difference in mortality between the 2 MTWA groups and the 2 QRS groups, the 2-year actuarial mortality rate was substantially lower among patients with normal MTWA test (3.8%), than among patients with a narrow QRS duration (12%), corresponding to false negative rates of 3.5% and 10.2% respectively (see below). A QRS duration >120 ms was weakly associated with MTWA status (OR 1.7, p=0.15). In a multivariate Cox model, MTWA remained a strong predictor of mortality after adjusting for QRS duration (hazard ratio 4.7, p=0.012).

Measure	MTWA	QRS Duration
Actuarial Mortality%		
Abnormal	17.8	15.9
Normal	3.8	12.0
Hazard Ratio	4.8	1.5
Classified as low risk (%)	32.2	68.2
False-negative rate (%)	3.5	10.2

The data from this study indicates that MTWA is a better than QRS duration in identifying high-risk patients among those with ischemic heart disease and left ventricular ejection fraction of $\leq$ 30% who fit MADIT II criteria.

Cohen also investigated the usefulness of MTWA in stratifying risk of the MADIT II population (Cohen, 2004). He prospectively evaluated nine studies done previously which had evaluated MTWA's role in predicting occurrence of VTE. These studies included a variety of patient populations (patients referred for electrophysiologic studies, patients with CHF, patients with dilated cardiomyopathies, and patients with myocardial infarctions), as well as a number of differing follow up periods (ranged from 13 to 72 months). The results of the analysis revealed that relative risk (RR) varied between 1.4 to 16.8 indicating that MTWA was an effective non-invasive means of assessing which patients were at high risk and low risk of VTE and sudden cardiac death. Cohen also noted a study performed by Hohnloser and associates that reported on 129 MADIT II type patients drawn from two previously published prospective studies which evaluated the use of MTWA as a predictor of VTEs (Hohnloser, Ikeda, Bloomfield, Dabbous, Cohen, 2003). These patient had previously had myocardial infarctions as well as ejection fractions < than 30%. This evaluation consisted of 87 patients that were taken from the Ikeda and colleagues study (Ikeda, Saito, Tanno, et al. 2002); while 42 participants were taken from the Klingenhaben and colleagues study (Klingenheben, Zabel, D'Agostino, Cohen, Hohnloser 2000). The primary endpoint of the study was sudden cardiac death. Sub-group analysis revealed that in this population at 24 months of follow up, there was a 15.6% rate of cardiac arrest and sudden cardiac death among participants that tested positive or indeterminate for MTWA, compared with no events among patients that tested negative for MTWA.

Grimm and colleagues evaluated a number of variables which were felt important in determining arrhythmia risk stratification for patients with dilated cardiomyopathy (Grimm, Christ, Bach, Müller, Maisch 2003). These factors included left ventricular ejection fraction and size by echocardiography, heart rate variability, baroreflex sensitivity, SAE, arrhythmias on Holter ECG, QTc, and MTWA using a spectral analysis algorithm. Of the 463 screen patients with IDC, 343 were enrolled, and of this number 263 patients with sinus rhythm. During the 52 month follow-up period, major arrhythmias were observed in 46 patients (13%), including sudden cardiac death in 23 patients. A total of 49 patients (14%) died during follow-up, and 10 patients (3%), underwent heart transplantation.

Major arrhythmic events occurred in 38 (14%) of the 263 patients with sinus rhythm at study entry. Univariate analysis revealed that left ventricular ejection fraction and diameter, non-sustained VT, and frequent ventricular premature beats on a 24-hour Holter ECG, and indeterminate MTWA were statistically associated with arrhythmic events during follow up. But multivariate analysis revealed only left ventricular ejection fraction was a significant predictor of major events during follow-up, with a relative risk of 2.28 per 10% reduction of ejection fraction. Multivariate analysis also revealed that left ventricular ejection fraction was a significant predictor of transplantation-free survival, with a relative risk of 2.51 per 10% decrease in ejection fraction. And for the 10% of patients with ICDs and atrial fibrillation at the entry to the study, multivariate analysis again revealed that left ventricular ejection fraction and the lack of beta-blockers were significant predictors of major arrhythmic events. Based on the multivariate analysis, MTWA was not found to be statistically associated with arrhythmic risk stratification.

Grimm does note discrepancies in results when compared to other studies evaluating the usefulness of MTWA. He attributes differing results due to a differences in methods and patient populations. In contrast to this study, other studies have used smaller patient populations as well as other studies allowing patients with sustained VT or VF. Also, Grimm notes that other studies most of the arrhythmic events during follow-up occurred in patients who had already received an ICD before study entry because of a history of sustained VT or cardiac arrest. The author did note some limitations of this study included fact that the use of beta-blockers was non-uniform and that many patients did not receive beta-blockers at the entry of the study. He also noted that even though this was a large study that included patients with Idiopathic cardiomyopathy for risk stratification, the number of events in the MACAS study may still be too small to exclude moderate relations of some of the variables tested to outcome with certainty.

4. MCAC

A Medicare Coverage Advisory Committee (MCAC) meeting was not convened on this issue.

5. Evidence-based guidelines

We did not find published evidence-based guidelines for MTWA.

6. Professional Society Position Statements

There were no published position statements on the use of MTWA as a diagnostic test from the American Heart Association, the American College of Cardiologist, the Heart Rhythm Society, or the American College of Chest Physicians. We did receive comments from several professional societies during the public comment period, as noted below.

7. Expert Opinion

We have not currently received any expert opinions on the use of MTWA testing for evaluating candidates for ICD placement.

8. Public Comments

During the initial public comment period, CMS received written statements from 28 sources including practicing cardiologists, professors of medicine at various university hospitals, cardiac devices manufacturers, and a summary comment from the requestor. Of these, 22 commented that MTWA is effective for risk stratification prior to ICD surgery and that the test should be covered nationally, without specifically commenting whether MTWA should be mandatory prior to ICD placement. Of these 22, nine also believed MTWA would be cost-effective by way of avoiding ICD placement in patients at low risk of SCD. One of these commenters expressed MTWA would be useful for identifying patients that would possibly benefit from ICD explantation or replacement, given recent reports of ICD malfunctions. This commenter also mentioned that MTWA might be useful for management of patients with ventricular arrhythmias. One submitted comment stated MTWA should be required to identify patients most likely to benefit from ICD therapy.

Of the three device manufacturers, one stated that an NCD on MTWA should be delayed until 2007 when results of an industry-sponsored prospective trial are released. Should CMS issue an NCD, this manufacturer believes that MTWA should not be a prerequisite for ICD therapy in the MADIT II and SCD-HeFT populations. A second manufacturer supports the decision reached by CMS in the ICD NCD whereby MTWA should be included in future clinical trials. They believe there is currently insufficient evidence that MTWA improves net health outcomes or that MTWA is reasonable and necessary for the indications requested by Cambridge Heart.

Two of the three manufacturers believe that the ICD NCD would need to be formally reconsidered for MTWA testing to become part of the ICD follow-on registry. One manufacturer believe that inclusion of MTWA in the registry be optional. Two manufacturers believe that coverage of MTWA should be based on Local Coverage Determinations, as it is currently. The comments from one manufacturer refer to a June 2005 press release by Blue Cross and Blue Shield Association’s Technology Evaluation Center which states there is insufficient evidence that use of MTWA testing improves net health outcomes or is as beneficial as other established clinical management.

The American College of Cardiology (ACC) was among those submitting public comments. The ACC stated that MTWA testing has potential risk stratifying value given the test’s high negative predictive value in select patients. However, the ACC believed that there currently is insufficient evidence to recommend MTWA testing for all patients being considered for ICD therapy, nor is the evidence adequate to require testing as a precondition of ICD therapy.

Public comments submitted by The Heart Rhythm Society (HRS) indicated that, until more data from prospective clinical trials is available, they could not recommend making MTWA a standard of care or to justify its use in risk stratification. The group could also not support making MTWA a required data element in the CMS National ICD Registry. HRS believes that MTWA may be useful is assessing ventricular arrhythmia risk in certain patient.

CMS utilizes the initial public comments to inform its proposed decision. We will respond in detail to the final public comments on this proposed decision.

VIII. CMS Analysis

National coverage determinations (NCDs) are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under title XVIII of the Social Security Act § 1869(f)(1)(B). In order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B, and must not be otherwise excluded from coverage. Moreover, with limited exceptions, the expenses incurred for items or services must be "reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member," according to §1862(a)(1)(A) of the Social Security Act. This section presents to agency's evaluation of the evidence considered and the tentative conclusions reached for the assessment questions.

1.

Is the quality of evidence adequate to conclude that MTWA testing can improve net health outcomes and is reasonable and necessary for Medicare patients who are candidates for ICD placement?

From the studies used to evaluate this technology, it does appear that the quality of evidence is adequate to conclude that MTWA testing using a spectral analysis algorithm can improve net health outcomes, and is reasonable and necessary for Medicare patients who are candidates for ICD placement. The reviewed literature contains a number of studies evaluating the use of MTWA in a variety of population settings, including subjects with congestive heart failure (CHF), ischemic CHF, non-ischemic CHF, dilated cardiomyopathy, hypertrophic cardiomyopathy, post MI, and in healthy subjects. The material reviewed included not only small prospective studies with a homogenous patient population, but also large systematic reviews with heterogeneous patient populations. Also included in this analysis were studies that looked specifically at MTWA's role as a risk stratification tool in patient populations similar to those in both MADIT II and SCD-HeFT.

A number of diagnostic tools are available for risk assessment. Unfortunately, some of these tools have low diagnostic usefulness. In order for a diagnostic test to be useful, it must be able to demonstrate accuracy and reliability. Commonly used measures of diagnostic accuracy include sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). Though some of the studies used in this assessment did not include these measures of accuracy, most did. When reviewing these measures of accuracy, MTWA demonstrated superior findings related to sensitivity and NPV when compared to other diagnostic tests used to assess risk of VTEs.

Across a number of population settings, MTWA consistently demonstrates superiority when compared to other diagnostic measures that assess risk of VTEs. Though some of the studies noted some limitations related to methodology as well as research design, these limitations were not enough to invalidate their findings.

We reviewed the BCBSA technology assessment. Both CMS and BCBA use an evidenced-based medicine approach, based on specific criteria, when assessing the effectiveness of technology. Though both CMS and BCBSA have similar criteria for assessing technology, CMS must also assure that the technology has demonstrated improved net outcomes within the Medicare-eligible population.

Due to the unique characteristics of the Medicare-eligible population (i.e. elderly, and more likely to have multiple co-morbidities), sudden cardiac death has a higher potential to occur as a result of VTE in this population. The potential harms from adverse events are also more likely to occur within this population. Because of these features of the Medicare population, the potential for benefit or harm from ICD placement varies from that of the BCBA population at large, and plays a prominent role in our decision making. Indications for ICD placement also differ between the two organizations. Because of the higher potential for VTE occurrence in the Medicare population, and because CMS recognizes VTEs as an indication for ICD placement, CMS feels that the use of MTWA is reasonable and necessary to address problems related to VTE and its adverse consequences.

Based on this analysis, CMS proposes that MTWA is a useful risk stratification tool and can identify which heart patients are at negligible risk of sudden death, and who may therefore be able to avoid ICD implantation and its attendant risks.

However, CMS does not believe that the evidence is sufficient to show that MTWA should be the only diagnostic test for the purpose of stratifying high risk patients of VTE. Physicians may choose to use a variety of other diagnostic testing to elucidate the need for an ICD (e.g., left ventricular ejection fraction, signal-averaged ECG, etc.). Also, we do not believe that the current evidence is sufficient to require that physicians use the results of MTWA testing to select appropriate patients for ICD implantation.

2.

If the evidence is adequate to conclude that MTWA testing can improve net health outcomes, what characteristics of the test method, the pathologic condition, or the patient can satisfactorily predict an improved health outcome?

Extensive clinical research has revealed that patients with symptoms of or at risk of life threatening arrhythmias who test positive for T-wave alternans are at a significant risk for subsequent development of sudden cardiac events, including sudden death, while those who test negative are a minimal risk. The use of MTWA using a spectral analysis algorithm as a stratification tool can help to identify patients in high risk population (e.g., those with ischemic and non-ischemic cardiomyopathy, dilated cardiomyopathy, post myocardial infarction, MADIT II-type, or SDC-HeFT-type) who are actually at low-risk for SCD. By applying this diagnostic tool, it is possible to classify those who test positive or indeterminate for MTWA (e.g., those more likely to benefit from ICD implantation), and those who test negative for MTWA (e.g., those less likely to benefit from ICD implantation).

Studies have demonstrated that ICD implantation does improve survival in patients prone to VTEs. Based on accuracy measures such as sensitivity and NPV, studies have demonstrated that, when it is applied to appropriate target populations, MTWA can identify those patients in which prophylactic ICD implantation is of little benefit, as well as the patient populations in which ICD implantation is beneficial.

The reviewed studies that mentioned a specific type of MTWA method all used the spectral analysis algorithm (including study performed by Grimm which failed to show any benefit in the use of MTWA). There are other methods which can be used to measure MTWA (e.g., modified moving average), though we found no peer-reviewed published articles discussing these algorithms at the time of our analysis. Currently the evidence only supports the use of spectral analysis algorithm for the detection of MTWA.

IX. Proposed Conclusion

CMS is seeking public comment on our proposed determination that there is sufficient evidence to conclude that the use of microvolt T-wave Alternans (MTWA) diagnostic testing is reasonable and necessary for the evaluation of Medicare beneficiaries at risk for sudden cardiac death (SCD). We are also proposing that MTWA diagnostic testing is only reasonable and necessary if measured employing the spectral analytic method.

We propose to issue a National Coverage Determination (NCD) that states: Microvolt T-wave Alternans diagnostic testing is covered for the evaluation of patients at risk of sudden cardiac death, only when the spectral analytic method is used.

We are requesting public comments on this proposed determination pursuant to section 731 of the Medicare Modernization Act. After considering the public comments and any additional evidence we will make a final determination and issue a final decision memorandum.

APPENDIX A [PDF, 117KB]

APPENDIX B

General Methodological Principles of Study Design
(Section VI of the Decision Memorandum)

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve net health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the generalizability of findings from individual studies to the Medicare population; and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.

- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

- Randomized controlled trials
- Non-randomized controlled trials
- Prospective cohort studies
- Retrospective case control studies
- Cross-sectional studies
- Surveillance studies (e.g., using registries or surveys)
- Consecutive case series
- Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess net health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

An intervention is not reasonable and necessary if its risks outweigh its benefits. Net health outcomes is one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

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[1] Huikuri, et al., 2001.

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